introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof is earnestly requested.

Upon entry of the amendments, claims 36-43 and 47-51 will remain pending in the application. Claims 36, 38, 41-43 and 47-48 are being amended. No claims are being added or canceled.

Exemplary support for the amendments to claims 36 and 42-43 exist in the specification at page 40, lines 24-35. All other amendments are discussed in detail below.

II. Terminal Disclaimer will Obviate the Double Patenting Rejection

Claims 36-41 remain rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-8 of U.S. Patent 5,851,999.

Applicants request that the Examiner hold this rejection in abeyance until the subject matter of claims 36-41 is otherwise deemed allowable. At that time, Applicants intend to submit a terminal disclaimer, which will obviate the rejection.

III. The Claims Comply with the Definite Claiming Requirement of 35 U.S.C. § 112

Claims 38-39, 41 and 47-48 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention. In particular, the Office asserted that (i) claim 38 contained an improper Markush group, (ii) claim 41 did not convey by what means the cell line expresses truncated Flk-1, and (iii) claims 47-48 suggest that the recited protein comprises a nucleic acid sequence.

As applied to the amended claims, these rejections are moot. First, amended claim 38 recites a proper Markush group in which the vector is a retrovirus vector, an adeno-associated viral vector *or* a herpes viral vector. Second, amended claim 41 recites that the cell line (i) produces infectious retrovirus particles encoding truncated Flk-1 and (ii) expresses truncated Flk-1 encoded by the retrovirus vector. Thus, it is clear that the Flk-1 expressed by the cell line is encoded by the retrovirus vector, and not some other source. Third, amended claims

47-48 clearly state that the claimed proteins comprise amino acids, not nucleic acids.

Therefore, Applicants respectfully request withdrawal of the indefiniteness rejections.

IV. The Invention is Patentable over the Cited Art

Claims 36-42 remain rejected and claims 47-51 are newly rejected as being obvious over Lemischka (U.S. 5,185,438), Matthews *et al.* ("Matthews") and Termen *et al.* ("Termen") in view of Ulrich *et al.* ("Ulrich") and Ueno *et al.* (including "Ueno-1" and "Ueno-2").

The Office alleges that the three primary references teach that Flk-1 is a VEGF receptor belonging to the class of type III tyrosine kinase receptors, with strong homology to the c-Kit family of receptors, and that Flk-1 DNA can be inserted into vectors. In particular, it states that Lemischka discloses soluble forms of the Flk-1 receptor and vectors containing the DNA, that Matthews discloses a recombinant vector comprising cDNA encoding Flk-1, and that Terman discloses cDNA encoding a receptor called KDR, a receptor of VEGF and the human homologue of Flk-1. The Examiner acknowledges, however, that none of these references teach or suggest constructing a recombinant vector encoding a truncated form of Flk-1 as recited in the rejected claims.

The Office further alleges that Ullrich and the two Ueno publications disclose three different receptor proteins that are truncated by the deletion of all or a portion of the intracellular domain. It then concludes that it would have been obvious for a person skilled in the art at the time of invention to modify the nucleic acids and recombinant vectors of the Lemischka, Matthews or Terman to delete all or a portion of the sequence encoding the intracellular domain, as taught by Ullrich or the Ueno publications.

As motivation to combine the teachings of the six cited references, the Office cites Terman's suggestion that Flk-1 is a homolog of the murine KDR receptor and that it would be "desirable to investigate the dimeric combinations in which the receptor occurs, and the relationship of such to the physiological responses known to occur in response to the ligand, VEGF . . . ." The Office also cites teachings from Ullrich and Ueno as providing motivation to combine the references.

Applicants respectfully traverse the rejection.

First, the rejection is improper as to claims 49-51, which are directed to a method of inhibiting the cellular effects of VEGF, not to recombinant vectors. Claims 49-51 depend from a claim (43) that already has been deemed allowable over the cited references. Because claims 49-51 further limit the subject matter of an allowable claim, they also are allowable.

Second, the rejection should not apply to the remaining claims. To form a proper basis for a rejection under 35 U.S.C. § 103, prior art must supply both a motivation for making the claimed invention and a reasonable expectation of success for obtaining the claimed invention. In the present case, the cited references would not motivate one skilled in the art to make a truncated Flk-1 receptor having a functional Flk-1 extracellular and transmembrane domain, and which inhibits the cellular effects of VEGF binding. Also, there was no expectation for success in making such truncated receptors at the time of invention.

Lemischka, Matthews and Terman purportedly describe cDNA sequences for wild-type Flk-1. None of these primary references, however, suggest the generation of truncated Flk-1 that has a functional extracellular and transmembrane domain. Moreover, none of these references suggests that expression of Flk-1 is specifically associated with endothelial cells or that a truncated Flk-1 could inhibit the cellular effects of VEGF binding.

Ullrich, Ueno 1 and Ueno 2 do not remedy the defects of the primary references. They describe various truncated receptor tyrosine kinases and show that early events in receptor tyrosine kinase signal transduction can be affected by such kinases in an artificial overexpression system. They do not, however, teach or suggest that truncated mutants would inhibit the biological response of endogenous receptors in a highly specific manner. Additionally, none of the references suggest that the truncated proteins are related to the Flk-1 receptor protein or that a truncated Flk-1 receptor protein would behave in a similar manner. Therefore, the references provide no reason for one skilled in the art to make truncated Flk-1 proteins of the present invention.

Indeed, it was entirely unexpected that truncated Flk-1 variants would have an inhibitory effect on the cellular response of VEGF and that polynucleotides encoding truncated Flk-1 variants would be useful for gene therapy of tumors by specifically inhibiting the growth of blood vessels *in vivo*.

Such results were unexpected because at least one other receptor, flt-1, was known to bind VEGF with high affinity. It also was known that flt-1 is expressed in endothelial cells of a growing tumor.[1] Significantly, flt-1 has a 50-fold higher affinity for VEGF than Flk-1.[2] Consequently, the skilled artisan would not have expected that blocking the Flk-1 signaling pathway would shut down the cellular response to VEGF, resulting in suppression of angiogenesis and inhibition of tumor growth. Rather, one of ordinary skill in the art would have anticipated that the biological response to VEGF, such as the proliferation of blood vessels, would still be transduced through flt-1. For at least this reason, the ability of the claimed truncated Flk-1 receptor proteins to inhibit angiogenesis were unexpected.

Thus, without Applicants' disclosure of the favorable properties of truncated Flk-1 receptor proteins, one skilled in the art would not have been motivated to make them or had any reasonable expectation of success for using them in any practical way. It therefore appears that the Office has used hindsight to provide a motivation to combine the primary and secondary references. This is improper, as the law clearly requires that, for a rejection under 35 U.S.C. § 103, both the motivation and reasonable expectation for successfully making an invention must be found within the prior art, and not be gleaned from Applicants' disclosure.[3]

Accordingly, Applicants respectfully request withdrawal of the rejection.

V. Concluding Remarks

Applicants believe that the application is in condition for allowance, and favorable reconsideration thereof is earnestly requested.

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[1] See, Plate *et al.*, 1992, Nature 359: 845-848; Plate *et al.*, 1993, Cancer research 53: 5822-5827.

[2] See, Waltenberger *et al.*, 1994, J. Biol. Chem. 269: 26988-26995.

[3] *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

If the Examiner believes that a telephone interview would advance prosecution, she is invited to contact the undersigned by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required in this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

11/12/03
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